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Interstitial Laser Treatment of the Ovary: An Experimental Study in Goats

Johan F. Beek, MD, PhD, Eugenie M. Kaaijk, MD,
Fulco van der Veen, MD, PhD, Karin de Boer, MD, PhD, Willem M. Ankum, MD, PhD,
Fibo J.W. ten Kate, MD, PhD, Frits B. Lammes, MD, PhD,
AND Martin J. C. van Gemert, PhD

Laser Center (J.F.B., E.M.K., M.J.C.v.G.), Departments of Gynecology and Reproductive Endocrinology (E.M.K., F.v.d.V., K.d.B., W.M.A., F.B.L.), and Pathology (F.J.W.t.K.), Academic Medical Center, Meibergdreef, 1105 AZ Amsterdam, The Netherlands

Background and Objective: **Interstitial laser treatment (ILT) of the ovary might be a new surgical approach to restore ovulation with a minimal risk of adhesion formation in patients with chronic hyperandrogenic anovulation who are unresponsive to hormone therapy. The objective was to investigate the feasibility of inducing a lesion limited to the center of the ovary in an animal model.**
Study Design/Materials and Methods: **ILT was performed in seven goats using Nd:YAG laser in combination with ultrasound monitoring. The extent of direct thermal damage was investigated in two goats, treating both ovaries during a laparotomy at 2, 4, 6, and 8 W, respectively, for 5 min. Adhesion formation was evaluated in five goats 81 days after an unilateral laparoscopic ILT at 1, 2, 4, 6, or 8 W for 5 min. During treatment temperatures on the surface of the ovary were measured.**
Results: **Histology after 1 day showed sharply demarcated necrotic lesions located centrally or subcapsularly at low powers, whereas at higher powers the lesions extended to the surface of the ovary. At low powers no adhesions were observed, whereas higher powers resulted in periovarian adhesions. Temperatures measured on the ovarian surface during treatment ranged between 38°C and 90°C. Ultrasound monitoring of the extent of thermal damage failed due to poor positioning.**
Conclusion: **Although this pilot study does not warrent firm conclusions, the results indicate that ILT of the ovary is feasible and that lesions without adhesions can be produced at low powers. The use of ultrasound to monitor the extent of thermal damage in the ovary should be a subject of further evaluation.**

Key words: adhesion formation, goat ovary, Nd:YAG laser, temperature, thermal damage, ultrasound

INTRODUCTION

Chronic hyperandrogenic anovulation (CHA) was originally described by Stein and Leventhal [1] as a syndrome consisting of amenorrhea, infertility, hirsutism, and bilateral enlarged cystic ovaries. However, the syndrome has a great variability in clinical and endocrinological presentation, the hallmark being chronic anovulation and the excess of ovarian androgen production. Infertility due to the anovulation is often the reason for seeking treatment. The first line of treatment for ovulation induction in patients with CHA is clomiphene citrate [2]. However, a

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Address reprint requests to Dr. Johan F. Beek, Laser Center, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.

significant number of patients are clomiphene resistant, and treatment with gonadotropins is cumbersome and often leads to multifollicular growth [2–4]. For many years wedge resection was a reasonable alternative to induce ovulation in these patients. Due to the high incidence of postoperative adhesion formation, thereby inducing a mechanical sterility, this surgical treatment has now become practically obsolete [5]. In the last decade, minimal invasive surgery using laparoscopic electrosurgery or laparoscopic laser surgery has been developed to restore ovulation with supposedly less adhesion formation. Although the results are encouraging, adhesion formation is still a drawback of these techniques [6].

The mechanism by which ovulation is restored using surgical techniques is not fully understood, but the main effect after the surgical techniques includes the reduction of ovarian androgen production, possibly due to the reduction of ovarian androgen producing tissue [7]. To minimize the risk of adhesion formation, reduction of the volume of androgen-producing tissue should theoretically be established with a minimal invasiveness and with minimal damage to the ovarian surface. We therefore propose to use an interstitial laser treatment (ILT) of the ovary to establish a volume reduction. Hypothetically, this treatment modality requires only one small lesion on the surface of the ovary for insertion of the laser fiber to coagulate ovarian tissue.

The aim of the present study was to investigate the feasibility of inducing a lesion limited to the center of the ovary in an animal model by using a Nd:YAG laser with various laser outputs. We studied (1) direct thermal effects and histology following laparotomic ILT, and (2) temperature changes on the surface of the ovary, the feasibility of monitoring the extent of thermal damage by means of ultrasound, histology and the occurrence of adhesion formation 12 weeks following laparoscopic ILT.

MATERIALS AND METHODS

Seven mature goats, weighing 40–45 kg, were used in this study. They were housed in groups and received standard goat feed daily and water ad libitum. The goats were fasted for 1 day prior to operation. The animals were premedicated with an intramuscular mixture of ketamin (4 mg/kg) and xylazin (0.05 mg/kg), and then intubated. General anesthesia was maintained with a halothane 0.5% and a NO_2/O_2 (3:2) mixture. Ringers glucose was administred intravenously. Postoperatively all animals received buprenorfine (0.005 mg/kg i.m.) and a profylactic dose of amoxycilline (15 mg/kg) for 1 week.

Surgery on all animals was performed by the same two surgeons (W.M.A., K. de B.) under standard aseptic surgical techniques. The animals were divided into two experimental groups. In group I (2 goats) a laparotomy was performed through a lower midline abdominal incision. Both ovaries were exposed and inspected, followed by insertion of a 17-gauge IVF needle (Cook, Queensland, Australia) in the center of one ovary. A 600-μm diameter quartz fiber coupled to a Nd: YAG laser (SLT, model CL 60, Malvern, PA) was inserted through this needle into the center of the ovary. The fiber guide, i.e., the IVF needle, was gently pulled back for ~1 cm (to prevent heat conduction along the needle tract) followed by laser irradiation. Both ovaries were treated this way, using 4 W and 8 W in the first goat, and 2 W and 6 W in the second goat with an exposure time of 5 min. A thermocouple (Fluke model 51, Everett, WA) was placed at the surface of the ovaries in the first goat; in the second goat a thermocamera (Inframetics model 600, Billerica, MA) was used to measure the temperature increase on the surface of the ovaries. Ultrasound monitoring was performed before, during, and after laser irradiation by means of a transcutaneous ultrasound probe (Pie medical model 400, 3.5 or 7.5 MHz, Maastricht, The Netherlands), which was pressed gently against the ovary. After the procedure, the abdomen was closed in three layers with sutures.

The goats were sacrificed 1 day after surgery. A relaparotomy was performed and the ovaries were inspected and removed. After fixation in formalin (10%), the ovaries were sectioned along the axis of the fiber optic tract and stained with haematoxylin and eosin for histopathological examination. In Group II (5 goats), a laparoscopy was performed. The goats were placed in supine position. An insufflation needle connected with an automatic CO_2 insufflator (Storz, Tuttlingen, Germany) was introduced in the peritoneal cavity to achieve and maintain a pneumoperitoneum. After having achieved sufficient pneumoperitoneum, one subumbilical trocar and two suprapubical trocars were introduced in the abdomen. The subumbilical trocar was used for a videolaparoscope. An atraumatic grasping forceps to fix the ovary during puncturing and laser irradiation, and a thermocouple (Fluke model 51) were inserted through two suprapubical trocards. The fi-

ber guide was introduced directly through the abdominal wall into the abdominal cavity under direct vision of the laparoscope. ILT was performed unilaterally in the largest ovary of each goat using powers of 1, 2, 4, 6, and 8 W for 5 min, respectively. The contralateral ovary served as a control. In the goat irradiated at 6 W, both ovaries were treated, due to difficulties with positioning of the fiber guide in the ovary that had been treated first. Puncture technique and insertion of the laser fiber in the center of the ovary in the goats were performed as described above. A transvaginal ultrasound probe (Pie Medical model 480, 3.5 MHz) was used in the goats treated with 2 W and 4 W to investigate the feasibility of monitoring thermal damage by ultrasound, whereas a laparoscopic ultrasound probe (Aloka Co., model 650, 7.5 MHz probe, Tokyo, Japan) was used in the goat treated with 6 W. After the procedure, the abdomen was closed with sutures.

The goats were sacrificed 81 days after surgery. Again, a laparotomy was performed directly after the animals were sacrificed, and the ovaries were inspected for adhesions and were resected thereafter for histopathological examination.

RESULTS

Direct Effects During ILT

In both groups no visible thermal changes on the surface of the ovaries were noticed at powers ≤4 W except for irradiation during laparotomy at 2 W (group I), where a small subcapsular zone of whitish coagulated tissue (diameter 3 mm) was noticed. At powers of 6 W and 8 W, we observed smoke development in both groups and, again, the development of a whitish zone of coagulation (maximal diameter 8 mm) on the surface of the ovaries along the fiber guide after 2 min of laser irradiation. Continued laser irradiation for 5 min at 6 W and 8 W resulted in a perforation of the surface of the ovaries opposite to the puncture site in all goats of both groups. In the laparoscopy group (group II), the creation of a perforation was complicated by a coagulation area on the adjacent uterus of one goat (8 W) and a carbonization spot on the peritoneum of another goat (6 W). After retraction of the fiber guide at the end of the procedure, bleeding of the ovary was observed at 8 W in one goat of the laparoscopy group (group II).

Ultrasound Monitoring

We did not succeed in ultrasound monitoring of thermal damage during ILT. Positioning of the ovaries against a transvaginal ultrasound probe during laparoscopic ILT was impossible without major tissue damage, and therefore transvaginal ultrasonography in goats proved unfeasible. Positioning of a transcutaneous ultrasound probe against the ovaries failed as well as this resulted in poor quality of the images before and during ILT. Eventually, adequate images of the ovaries were obtained by making use of a laparoscopic ultrasound probe, and during ILT at 6 W a small hyperechogenic area with a maximum diameter of 8 mm developed around the fibertip.

Temperature Measurements, Adhesion Formation, and Histology

The results of temperature measurements during ILT, as well as adhesion formation and histology at 1 day (group I) and 81 days (group II) after ILT, are summarized in Table 1.

In the laparotomy group (group I), measurements with the thermocamera at 2 W showed that the temperature of the ovary was <44°C after 2.5 min. At 5 min, a maximum local temperature of 62°C was measured; the surface temperature of most of that ovary remained at <44°C. The localization of this hot spot corresponded macroscopically with a whitish zone of coagulation as described above. At 6 W, a hot spot of 70°C was measured at 2 min and a hot spot of 90°C at 5 min. At 8 W, the temperature measured with a thermocouple was only 38°C. This difference was most likely caused by positioning of the thermocouple in the lower temperature region.

In the laparoscopy group (group II), no visible adhesions were present around the ovaries at the time of the initial procedures. The development of extensive periovarian adhesions were seen only in goats irradiated with 6 W and 8 W. One ovary of the goat treated bilaterally with 6 W showed severe atrophy. Adhesion formation did not occur in the opposite ovaries that served as controls. Histologic examination of the ovaries in the laparotomy group showed well-defined lesions in all ovaries 1 day after ILT. The lesions were sharply demarcated from normal ovarian tissue by a hyperemic zone. At 81 days after ILT, no visible damage was found in the ovary treated with 1 W. Lesions were probably absent, but also could have been missed due to incomplete sectioning of the ovaries.

DISCUSSION

In this study, ILT of the ovary was investigated in goats. ILT is a relatively new treatment

TABLE 1. Maximum Temperature Measurements, Adhesion Formation, and Histology in Group I and Group II Goats

Procedure	Power (W)	Maximum T (°C)	Evaluation (days)	Adhesions	Histology of lesion: shape and localization	Histology of lesion: maximal diameter/ length	Histology of lesion: type of damage
Laparotomy group (n = 2)	2	62[a]	1	n.a.	Subcapsular, oval-shape lesion, small zone of capsular necrosis	8 mm	coagulation
	4	77.0	1	n.a.	Central, oval-shape lesion, no capsular necrosis	12 mm	central cavitation and carbonization
	6	90[a]	1	n.a.	Rod-shape lesion with extensive capsular damage	16 mm	central cavitation and carbonization
	8	38	1	n.a.	Rod-shape lesion with extensive capsular damage	17 mm	central cavitation and carbonization
Laparoscopy group (n = 5)	1	39	81	−	n.a.	n.a.	no lesion found
	2	39	81	−	central	n.a.	focal areas of fibrosis
	4	40	81	−	central	n.a.	focal areas of fibrosis
	6	52	81	+	n.a.	n.a.	severe atrophy with some carbonization
	6	51	81	+	n.a.	n.a.	no lesion found
	8	62	81	+	central	8 mm	coagulation and carbonization

[a]Thermocamera.
n.a. = not applicable.

modality in medicine and is particularly used at low powers (1–5 W) with various exposure times (5–40 min) to induce necrosis of tumors and metastases in brain, breast, liver, and pancreas [8–11]. This form of treatment is also used for benign tumors such as hemangioma [12]. To the best of our knowledge, this is the first report suggesting to use ILT for treating a hormonal disorder.

In this study, powers ≤4 W show optimal results, as with these powers central or subcapsular coagulation zones were established with minimal capsular damage and no adhesions were seen 81 days after ILT. We also used powers >4 W. These relatively high powers of 6 W and 8 W were chosen on purpose. First, the relative whitish ovarian tissue was expected to have a low absorption at 1,064 nm and it was thought that higher powers might be required to establish sufficient thermal damage. Second, we considered it important to assess the extent of thermal damage and the treshold of the adhesion formation. ILT at 6 W and 8 W resulted in an extensive capsular damage, in a rapid temperature increase on the surface, in tissue damage outside the ovaries, and in extensive adhesion formation 3 months after ILT. These powers are obviously too high for central coagulation of goat ovaries.

There are two major risks of ILT of the ovaries: thermal necrosis of the intestines and hilus destruction causing atrophy of the ovary. To avoid thermal necrosis of the intestines, the temperature rise on the surface of the ovary during ILT should be minimal. In the laparoscopy group, the measured surface temperature was ≤40.5°C at powers ≤4 W. However, in the laparotomy group a maximum temperature of 62°C at 2 W was measured as a hot spot with the thermocamera, whereas the rest of the ovarian surface remained <44°C. This suggests that local hot spots in the laparoscopy group might have been missed with the thermocouple measurements and that for goat ovaries 2–4 W for 5 min might result in damage to surrounding tissue. However, we have to emphasize that goat ovaries are much smaller

(~2×1.5×1.5 cm) than human polycystic ovaries (~4×3×3 cm).

In this study, atrophy of one ovary occurred after ILT at 6 W. Hilus destruction of the ovaries can be another serious complication of ILT and might result in castration if both hili of both ovaries are destructed. To prevent this complication, positioning of the laser fiber close to the hilus should be avoided.

To prevent these complications, exact positioning of the fiber tip is mandatory. From experience with transvaginal puncturing of the ovary under ultrasound guidance for in vitro fertilization, we know that exact positioning of a needle in the center of the ovary is technically easy, which offers the possibility to confine thermal damage to the center of the ovary. In contrast to other experimental studies using ILT in the breast, liver, and pancreas [9–11], we did not succeed in monitoring thermal damage by ultrasound. In the liver, the extent of thermal damage produced by the Nd:YAG laser is visible by a hyperechogenic zone, which develops around the fibertip during ILT [9–11, 13]. The diameter of the echoscopic changes correlates well with the histopathological findings [13]. We failed to acquire adequate images with the transcutaneous and transvaginal ultrasound probe and therefore failed to monitor the extent of thermal damage using these probes. With the laparoscopic ultrasound probe, positioning was adequate and the development of a hyperechogenic zone around the fiber tip during laser irradiation could be visualized. We were unable to correlate the extent of these ultrasonic changes to histology, as the goat in the laparoscopy group (group II) survived for 81 days to evaluate adhesion formation. As it is of utmost importance to confine thermal damage to the center of the ovary and to avoid damage of the ovarian capsule, hilus, and to adjacent intestines, ultrasound monitoring of thermal damage should be the subject of further investigations.

In conclusion, preliminary data show that powers ≤2 W delivered for 5 min result in an intraovarian lesion with only a minimal capsular damage, a minimal increase in surface temperature, and no adhesion formation. Hypothetically, ILT of the ovary might be a new minimal invasive technique to reduce the ovarian androgen producing tissue and to restore ovulation with a minimal risk of adhesion formation. However, more animal experiments are needed to assess safety, the feasibility of monitoring of thermal damage during ILT of the ovary, and adhesion formation at low powers before a clinical trial can be performed.

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